

Topical Application of Oxybutynin Chloride Gel for Systemic Absorption

Inventors: Chin-Chih Chiang, West Covina, California

Harvey Tong, Taipei, Taiwan

Assignee: To be determined

ABSTRACT

Disclosed are gel formulations of oxybutynin chloride for systemic absorption. Pharmacokinetic parameters of the gel product on human volunteers are compared with those after oral administration of Ditropan XL 10 mg. C_{max} is similar after both dosage forms. However, t_{max} is shorter and half-life is longer for gel product. The gel product is to be applied once daily for the treatment of overactive bladder.

— Claims, 1 Drawing

Claims:

1. A method to deliver oxybutynin into blood to reach therapeutic blood levels by topical application.
2. A formula of ethanol or isopropanol based gel.
3. A formula using Propylene Glycol Laurate as a skin permeation enhancer.

Description

Basic information of Oxybutynin Chloride product :

Chemical Formula: α -Cyclohexyl- α -hydroxy-benzeneacetic acid 4-(diethylamino)-2- butynylester hydrochloride

Empirical Formula: $C_{22}H_{32}ClNO_3$

Molecular Weight: 393.95

Indications: Indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Dosage Form and Dose:

Syrup 5 mg/5 mL

Tablet 2.5mg or 5 mg, 2-3 times every day

SR Tablet 5 mg, 10 mg or 15 mg, once a day

(Current dosage form of Oxybutynin Chloride is oral.)

Oral bioavailability of Oxybutynin Chloride is 6%, most of the parent compound can not reach into blood. In addition, its metabolite, desethyloxybutynin is contributed to the side effects such as dry mouth, constipation and headache. These side effects can be minimized by bypassing hepatic metabolism which is normally the case after oral administration. The absorption of oxybutynin through skin provides an alternative route of drug delivery to bypass hepatic metabolism.

Oxybutynin Chloride is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. This kind of product can be commonly used for the treatment senile and patients on long journey. Due to the prolongation of human life span, senile population is increasing. Globalization results in heavier traveling and longer time of transportation. The need for the treatment of overactive bladder syndromes has a trend to increase. Current, oxybutynin is available in oral dosage form. The reasons of developing an oxybutynin chloride topical product to replace the oral product are as such.

1. Direct skin absorption will bypass first hepatic metabolism of oxybutynin. The major metabolite of oxybutynin is desethyloxybutynin which is responsible for the major side effect such as dry mouth.
2. Skin absorption has a sustained effect. It is used once daily. It is convenient to use, especially for

long term uscrs.

3. It is more convenient for elderly and patients with swallowing difficulties.
4. It shows fewer effects on liver and is more suitable for patients with liver dysfunction. No need to adjust doses.
5. The skin absorption is less affected by co-administration with food. It can be administered to the patients who are treated with other drugs.
6. Gel product is less skin irritating than patch product.

EXPERIMENTAL

Analytical

Oxybutynin concentrations in the in-vitro skin samples were assayed by HPLC. Reversed phase column was used.

In-vitro Skin Permeation through Human Cadaver Skins

Franz diffusion cells were used for in-vitro skin permeation studies. Distilled water was used as a receptor vehicle and maintained at 37°C by circulation water. Gel formulation was dosed at 0.1 mL on the epidermal layer of skins. Skin permeation was run for 24 hours. Oxybutynin concentration in the receptor vehicle was assayed by HPLC.

Preparation of Gel Product

1. Add propylene glycol into a container with water.
2. Slowly disperse Carbopol ETD 2020 into Step 1 solution.
3. In a separate container, mix isopropanol and other ingredients until homogeneous.
4. Add the solution of Step 3 into the solution of Step 2 and mix well.
5. Slowly add oxybutynin chloride into the solution of Step 4 until homogeneous.
6. Titrate the solution of Step 5 with alkalinizing agent until pH 6.5-7.5

Formulation Study and In-Vitro Skin Permeation

Lauroglycol (Propylene glycol laurate) is a water insoluble vehicle widely used as a skin permeation enhancer. In order to dissolve lauroglycol in the gel formulation at 5% level, it is necessary to add lecithin that functions as an emulsifier or solubilizer. Results of Table 1 indicate that ETD2020 is a better gelling agent than Pemulen TR-1NF (comparing OXY004-067a to OXY004-067b). In addition, isopropyl myristate at 1.5% is a better enhancer than lauroglycol at 5% level with lecithin used as a solubilizer (comparing OXY004-067a to OXY004-067c).

Table 1. Effect of Gelling Agent and Enhancers on Skin Permeation

Ingredient	OXY004-067a	OXY004-067b	OXY004-067c
	% (w/w)	% (w/w)	% (w/w)
Distilled water	40.0	34.0	34.0
ETD2020	1.0	---	1.0
Pemulen TR-1NF	---	1.0	---
Propylene Glycol	2.0	2.0	2.0
Isopropanol	53.0	53.5	53.5
Isopropyl Myristate	1.5	---	---
Lauroglycol	---	5.0	5.0
Lecithin	---	2.0	2.0
Oxybutynin Chloride	1.0	1.0	1.0
2-Amino-2-methyl-1-propanol	1.5	1.5	1.5
Skin Permeation Rate [(mg/10 cm ² /day, Avg±Std (%RSD, n=3)]	0.31±0.09 (28.4%)	0.11±0.06 (53.5%)	0.07±0.03 (38.3%)

Both isopropyl myristate and lauryl lactate are used as skin permeation enhancers. Table 2 shows that isopropyl myristate enhances more permeation of oxybutynin than lauryl lactate.

Table 2. Effect of Enhancers on Skin Permeation

Ingredient	OXY004-078c	OXY004-078d
	% (w/w)	% (w/w)
Distilled water	38.0	40.0
ETD2020	1.0	1.0
Propylene Glycol	4.0	2.0
Isopropanol	53.0	53.0
Isopropyl Myristate	1.5	---
Lauryl Lactate	---	1.5
Oxybutynin Chloride	1.0	1.0
2-Amino-2-methyl-1-propanol	1.5	1.5
Skin Permeation Rate [(mg/10 cm ² /day, Avg±Std (%RSD, n=3)]	0.21±0.03 (16.1%)	0.16±0.07 (41.1%)

Comparing the results of OXY004-079c and OXY004-079d, it is found that addition of Tween-80 does not promote the skin delivery of oxybutynin. Increase concentration of isopropyl myristate in the formulation does not necessary increase the permeation of oxybutynin (comparing OXY004-079d to OXY004-079g). Again, ETD2020 is a better gelling agent than Pemulen TR-1NF (comparing OXY004-079d to OXY004-079h).

Table 3. Effect of Gelling Agent and Enhancers on Skin Permeation

Ingredient	OXY004-079c	OXY004-079d	OXY004-079g	OXY004-079h
	% (w/w)	% (w/w)	% (w/w)	% (w/w)
Distilled water	40.0	40.0	39.0	39.0
ETD2020	1.0	1.0	1.0	---
Pemulen TR-1NF	---	---	---	1.0
Propylene Glycol	4.0	2.0	4.0	2.0
Isopropanol	52.5	53.0	50.5	50.5
Isopropyl Myristate	1.5	1.5	5.0	5.0
Tween-80	0.5	---	---	---
Oxybutynin Chloride	1.0	1.0	1.0	1.0
2-Amino-2-methyl-1-propanol	1.5	1.5	1.5	1.5
Skin Permeation Rate [(mg/10 cm ² /day, Avg±Std (%RSD, n=3)]	0.12±0.03 (24.0%)	0.24±0.05 (21.7%)	0.11±0.02 (22.1%)	0.10±0.07 (65.8%)

Results as shown in Table 4 indicate that the addition of 2% menthol in OXY004-088b decreases 33% the skin permeation of oxybutynin as compared to OXY004-088a.

Table 4. Effect of Menthol on Skin Permeation

Ingredient	OXY004-088a	OXY004-088b
	% (w/w)	% (w/w)
Distilled water	40.0	38.0
ETD2020	1.0	1.0
Propylene Glycol	2.0	2.0
Isopropanol	53.3	53.3
Lauroglycol	1.5	1.5
Menthol	---	2.0
Oxybutynin Chloride	1.0	1.0

2-Amino-2-methyl-1-propanol	1.2	1.2
Skin Permeation Rate [(mg/10 cm ² /day, Avg±Std (%RSD, n=3)]	0.57±0.06 (10.1%)	0.36±0.19 (53.5%)

Formulation of Oxybutynin Gel 1%

Ingredient	% (w/w)	1 kg Batch (gm)
Water	44.0	440
Propylene Glycol	2.0	20
Carbopol ETD2020	1.0	10
Isopropanol	50.0	500
Lauroglycol	1.0	10
Oxybutynin Chloride	1.0	10
Diisopropanolamine	1.0	10
Sum	100.0	1000
pH	7.0-8.5	

Formulation of Oxybutynin Gel 3%

Ingredient	% (w/w)	1 kg Batch (gm)
Water	40.0	400
Propylene Glycol	2.0	20
Carbopol ETD2020	1.0	10
Isopropanol	50.0	500
Lauroglycol	1.0	10
Oxybutynin Chloride	3.0	30
Diisopropanolamine	3.0	30
Sum	100.0	1000
pH	7.0-8.5	

Pharmacokinetic studies

Oxybutynin gel 1% and 3% were studied on human volunteers.

Pharmacokinetic Parameters after single Oral Dose of Ditropan XL 10mg (n=43)* and those after Gel Applications (n=3)

	DITROPOAN XL 10 mg			Gel 1%	Gel 3%
Paramcters	R-Oxybutynin	S-Oxybutynin	Total	Oxybutynin	Oxybutynin
C _{max} (ng/mL)	1.0±0.6	1.8±1.0	2.8	1.41±0.59	3.47±1.39
t _{max} (hr)	12.7±5.4	11.8±5.3	~12	6.67±3.06	4.00
t _{1/2} (hr)	13.2±6.2	12.4±6.1			21.5±0.8
AUC ₍₀₋₄₈₎ (ng·hr/mL)	18.4±10.3	34.2±16.9	52.6	21.0±2.7	54.7±8.4
AUC _{inf} (ng·hr/mL)	21.3±12.2	39.5±21.2	60.8	33.6±12.9	61.8±9.9

* Physicians' Desk Reference, p. 2453, 57 Edition, 2003.

Study Design of Gel 1% (PK 1)

Study Purposes	Study Design	Chemical assayed	Parameters to evaluate
To study the pharmacokinetic parameters of oxybutynin after topical applications	- 5 gm of gel applied - Volunteers: male (3) - Application site: abdomen	Oxybutynin	C _{max} t _{max} t _{1/2} AUC ₍₀₋₄₈₎ AUC _{inf}

Study Design of Gel 3% (PK 2)

Study Purposes	Study Design	Chemical assayed	Parameters to evaluate
To study the pharmacokinetic parameters of oxybutynin after topical applications	<ul style="list-style-type: none">- 5 gm of gel applied- Volunteers: female (3)- Application site: abdomen	Oxybutynin	C_{max} t_{max} $t_{1/2}$ $AUC_{(0-48)}$ AUC_{inf}